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Which patients with myelofibrosis should receive ruxolitinib therapy?

ELN-SIE evidence-based recommendations

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ABSTRACT

Ruxolitinib is an oral JAK1/JAK2 inhibitor approved for the treatment of patients with myelofibrosis (MF) based on the results of two randomized clinical trials. However, discordant indications were provided by regulatory agencies and scientific societies for selecting the most appropriate candidates to this drug. The European LeukemiaNet and the Italian Society of Hematology shared the aim of building evidence-based recommendations for the use of ruxolitinib according to the GRADE methodology. Eighteen patient-intervention-comparator-outcome profiles were listed, each of them comparing ruxolitinib to other therapies with the aim of improving one of three clinical outcomes: a) splenomegaly, b) disease-related symptoms, and c) survival. Ruxolitinib was strongly recommended for improving symptomatic or severe (>15 cm below the costal margin) splenomegaly in patients with an IPSS/DIPSS risk INT2 or high. Ruxolitinib was also strongly recommended for improving systemic symptoms in patients with a MPN10 score higher than 44, refractory severe itching, unintended weight loss not attributable to other causes or unexplained fever. Because of weak evidence, the panel does not recommend ruxolitinib therapy for improving survival. Also, the recommendations given above do not necessarily apply to patients who are candidates for allogeneic stem cell transplant.

INTRODUCTION

In the last 20 years the outcomes of blood cancers in Europe have significantly improved¹ proportionally to the number of newly approved agents^{2,3}. In 2012 two randomized phase 3 clinical trials reported outcomes for myelofibrosis (MF) patients treated with ruxolitinib, a JAK1/JAK2 inhibitor^{4,5}. Ruxolitinib therapy was associated with reduction in splenomegaly and improvement of MF-related symptoms and, on this basis, it was rapidly approved in the US and EU. Three years later, however, the Cochrane Collaboration cast doubts on the real efficacy of this drug since a systematic literature review based on a limited follow-up concluded that ruxolitinib did not demonstrate sufficient efficacy for the two principal outcomes⁶. Availability of ruxolitinib in clinical practice, prompted the British Society of Haematology⁷, the European Society of Medical Oncology⁸ and the Australian Hematology Association⁹ to elaborate recommendations on its use, although they were not based on an explicit GRADE approach.¹⁰ As a matter of fact, differences between marketing authorization for ruxolitinib and patient selection criteria for the COMFORT trials were reckoned as relevant hurdles by the National Institute for Clinical Excellence, which finally approved ruxolitinib in 2016 but within strict evidence-based stonemarks.¹¹ In August 2015, the Italian Society of Haematology (SIE) and the European LeukemiaNet (ELN) shared the common effort of providing clinicians with strictly evidence-based recommendations for the selection of MF patients suitable for Ruxolitinib therapy. This paper reports the process for elaborating such statements according to the GRADE methodology and the final recommendations of the expert panel.

MATERIALS AND METHODS

A multi-country panel of 12 senior ELN members with expertise in MF management was convened. A hematologist with expertise in development of clinical practice guideline led the group through the following steps, according to the GRADE methodology¹⁰:

1. Listing the three most relevant efficacy outcomes and the two most relevant risk outcomes
 - a. Efficacy outcomes: the panel chose splenomegaly, disease-related symptoms and overall survival
 - b. Risk outcomes: the panel chose bleeding and infection
2. Listing therapies to be compared with ruxolitinib for the achievement of each specific clinical outcome
 - a. Comparator therapies were hydroxycarbamide (HU) and interferon (IFN)
 - b. Prednisone was also considered a comparator therapy for the outcome “disease-related symptoms”

3. Formulating an agreed definition for ambiguous terms:
 - a. “symptomatic” splenomegaly
 - b. “severe” splenomegaly
 - c. “relevant” disease-related symptoms
4. Listing patient-intervention-comparator-outcome (PICO) vignettes (Table 1)
5. Critical appraisal of available evidence for each of the PICOs
 - a. Available evidence was retrieved from the following sources: PubMed, ASH proceedings from 2013 ahead and EHA proceedings from 2013 ahead
 - b. Evidence was appraised according to the following hierarchy:
 - i. Comparative studies with appropriate directness, i.e. control arm corresponding to the comparator treatment of the PICO
 - ii. Comparative studies without appropriate directness, i.e. control arm does not correspond to the comparator treatment of the PICO
 - iii. Non-comparative studies
6. Assessing the net benefit of ruxolitinib versus the comparator treatment in each PICOs
7. Assessing the quality of evidence according to GRADE, namely based on:
 - a. The study design (see hierarchy above)
 - b. The study directness, namely the degree of similarity between the study and PICO population, intervention and outcome
8. Scoring 1 to 9 the preference of each panelist for ruxolitinib versus the comparator therapy within each PICO
9. Formulating final recommendations
10. Assessing the strength of approved recommendations, according to GRADE, namely based on the following criteria:
 - a. Quality of evidence
 - b. Benefit-to-risk balance
 - c. Overall uncertainty

A Delphi panel method¹² was used for the steps 1, 2, 3 and 8. Final approval of definitions and recommendations was achieved informally during three meetings held in Orlando in December 2015, in Mannheim in February 2016, and in Milan in March 2016.

RESULTS

Splenomegaly

Summary of evidence

The body of evidence supporting PICOs one to six mainly consisted of the COMFORT II trial, randomizing intermediate-2 and high risk MF patients to ruxolitinib or best-available therapy (BAT).⁴ The clinical outcomes of patients assigned to BAT and receiving active treatments (mostly HU) was considered a proxy for the clinical outcomes of HU-treated control patients. The COMFORT II trial reported that in patients assigned to ruxolitinib spleen volume decreased, on average, by 29% in a median of 12 weeks.^{4,13} The probability of maintaining a -35% reduction in spleen volume was 48% at five years, that is a median time of response of 3.2 years.¹³ Rather, palpable spleen size decreased for a few months and by no more than 10 cm in a small portion of actively treated patients assigned to BAT: in these patients spleen volume increased by 5% in a year.¹⁴ The efficacy of ruxolitinib onto spleen size was also supported by the randomized trial COMFORT I,⁵ the prospective study ROBUST¹⁵ and the large phase IIIb study JUMP¹⁶. A definite dose-response was reported.

Due to the scarce number of IFN-treated patients enrolled into the COMFORT-II control arm, evidence from phase II and retrospective studies was sought. One hundred and twenty-six patients reported by mainly retrospective studies were recently reviewed.¹⁷ Spleen response rates reported by the largest studies ranged from 30% to 53%, and median time to response was greater than 6 months.¹⁷⁻²⁰

Finally, we scanned evidence for patients with intermediate-1 risk disease, who were excluded from enrollment into the COMFORT trials: phase II¹⁵ and phase IIIb¹⁶ studies reported a similar efficacy of ruxolitinib onto splenomegaly in this subpopulation than in patients with intermediate-2 or high risk disease.

Quality of evidence

The overall quality of evidence supporting the net benefit of ruxolitinib in PICOs 1 to 6 was judged to be high in principle, due to the randomized design of the COMFORT II trial, but it was necessarily reduced to low or very-low due to unblindness and serious indirectness of the study. Serious indirectness was caused by a limited portion (47%) of the control arm patients being treated with HU (the comparator therapy in PICOs 1 and 2) and by a very small portion of cytoreduction-naïve patients (population of PICOs 1 to 4). The quality of evidence supporting PICOs 2 to 6 was limited by the very few patients receiving interferon in the BAT arm of the COMFORT II trial and by the scarcity of evidence supporting interferon efficacy in prospective or comparative studies. However, indirectness was also supported by the lack of information regarding spleen size kinetics before enrollment (population of PICOs 2, 4 and 6)

and of sub-analyses for patients with symptomatic splenomegaly at enrollment (population of PICO 1,3 and 5). The quality of evidence was increased by a clear demonstration of a dose-response relationship between ruxolitinib dose and spleen volume reduction.

Finally, the quality of evidence of ruxolitinib as compared with HU for patients with intermediate-1 risk disease was judged to be very low due to the non-randomized design of the studies supporting the safety and efficacy of ruxolitinib in this setting.

Panel discussion

The panel agreed that patients with symptomatic and/or severe splenomegaly not responding to prior treatment should receive ruxolitinib, based on the rapid and durable reduction of spleen size reported by the COMFORT trials.^{4,5,13} The panel deemed that cytoreduction-naïve patients with symptomatic or severe splenomegaly, who also need a rapid and sustained spleen reduction, were expected to get from ruxolitinib a similar incremental benefit as pre-treated patients.

Despite the lack of comparative evidence, the panel also recommended ruxolitinib in a limited subset of patients with intermediate-1 risk disease whose quality of life is severely impaired by huge symptomatic spleens or splenomegaly-related symptoms not responsive to prior therapies.

Finally, the panel did not provide any operative definition for “progressive splenomegaly”, however, it deemed that treatments aimed at preventing severe or symptomatic splenomegaly might be effectively implemented in patients with progressive increase of spleen size, although no evidence from clinical trials supports a specific treatment pathway.

Recommendations

Although evidence suggests that ruxolitinib is effective in reducing splenomegaly in any patient risk category, the benefit/risk profile of the drug favors its use for improving splenomegaly in selected patients.

Ruxolitinib is recommended for improving splenomegaly in:

- Patients with intermediate-2 or high risk disease and either symptomatic or severe splenomegaly (strong recommendation)*

- Patients with intermediate-1 risk disease and either symptomatic or severe splenomegaly not responsive or intolerant to HU or interferon (weak recommendation)*

- Patients with intermediate-1 risk disease and both symptomatic and severe splenomegaly not previously treated with any cytoreductive agent (weak recommendation)*

“Severe” splenomegaly refers to splenomegaly palpable 15 cm below the costal margin.

“Symptomatic” splenomegaly refers to the concurrent presence of a splenomegaly and local

symptoms not attributable to other causes, such as pain in the left upper quadrant of the abdomen, or impairment of food intake due to early satiety.

Disease-related symptoms

Summary of evidence

Only one study provided direct evidence of ruxolitinib relative efficacy in improving disease-related symptoms as compared with other therapies in patients with intermediate-2 or high- risk disease: COMFORT II trial reported a similar mean improvement of EORTC Q-C30 score at week 24 in patients assigned to ruxolitinib or BAT, provided that the latter were receiving an active treatment.¹⁴ Moreover, no dose-response relationship was proved by any comparative or non-comparative study. Nevertheless, a rapid, relevant and sustained improvement of fatigue, appetite loss and itching was consistently reported with ruxolitinib treatment by the COMFORT I and ROBUST trials.^{5,15} Appetite loss and dyspnea, on converse, significantly worsened in BAT-treated patients.¹⁴ Despite the universal use of EORTC Q-C30, the questionnaire is not disease-specific and includes 30 items, therefore it cannot be feasible outside a clinical trial setting. Rather, MPN10 (Table 2) is a brief disease-specific tool applied longitudinally in the COMFORT-I trial and validated in several languages, showing a good feasibility. Moreover, MPN10 score should be recorded in order to assess response according to IWG-MRT criteria. Despite no “clinically meaningful” threshold score for MPN10 has been validated, one third of MF patients enrolled in a cross-sectional study reported a MPN10 score higher than 44, which can be considered a good cut-off for selecting patients with “relevant” disease-related symptoms, in that it corresponds to the mean value plus one standard deviation.²¹

No study longitudinally assessed quality of life in patients receiving interferon or prednisone.

Patients with intermediate-1 risk disease enrolled into the ROBUST phase II trial achieved similar symptom improvement during ruxolitinib therapy than intermediate-2 and high risk patients.¹⁵

Quality of evidence

The overall quality of evidence was judged to be low. Despite the randomized design of the COMFORT II trial, several limitations hamper its quality in supporting PICO 7 to 9: limited size, unblindness, high rate of missing data and indirectness add up with lack of a clear-cut improvement in quality of life of patients assigned to ruxolitinib as compared with those assigned to active BAT. However, the consistency of the data reported by COMFORT II and other studies, namely, COMFORT I and ROBUST, supports a potentially relevant effect of ruxolitinib in the patients' quality of life.

Panel discussion

157 The panel deemed that a systematic and quantitative assessment of MF-associated symptoms with
158 MPN10 was feasible and necessary prior to treatment decisions. The panel also considered the
159 structured summary of evidence and the poor quality of the evidence supporting a benefit of ruxolitinib
160 as compared with BAT, mainly HU. However, the rapid and sustained action of ruxolitinib upon itching,
161 appetite and fatigue was considered to be sufficient to strongly recommend it in patients carrying a high
162 burden of symptoms, that is to say, with a MPN10 score higher than 44. The panel also deemed that
163 ruxolitinib could be recommended for controlling some specific severe symptoms, such as itching,
164 relevant weight loss or fever, irrespectively of the overall MPN10 score. The recommendation was
165 judged to be valid also in patients with intermediate-1 risk disease, while no exclusion criterion for low-
166 risk patients was required, since disease-related symptoms are very rare in this setting and would often
167 mean that patient risk category is increasing.

168 *Recommendations*

169 *Accurate assessment by the tools such as MPN10 should be performed before any clinical decision*
170 *regarding the use of ruxolitinib for improving disease-associated symptoms.*

171 *Ruxolitinib is recommended for improving disease-related symptoms in patients with a MPN10 score*
172 *higher than 44 or refractory severe itching (score >6) or unintended weight loss (>10% in the last 6*
173 *months) not attributable to other causes or unexplained fever (Strong recommendation).*

174 Survival

175 *Summary of evidence*

176 Search for evidence supporting PICOs 10 to 18 could retrieve only one study comparing the survival of
177 ruxolitinib-treated patients with the survival of patients assigned to other active treatments. The
178 COMFORT II trial reported a significant and relevant increase of five-year survival from 44% (BAT) to 56%
179 (ruxolitinib), despite cross-over, in patients with intermediate-2 or high risk disease. Spleen response
180 predicted a major improvement of survival.²² A survival benefit in favor of ruxolitinib versus other
181 therapies, consisting mainly of HU, was also reported by two case-control studies.^{23,24}

182 No evidence compared the overall survival of ruxolitinib-treated with interferon-treated patients.

183 No study longitudinally compared the overall survival of intermediate-1 patients receiving ruxolitinib
184 rather than other treatments.

185 *Quality of evidence*

186 The quality of evidence for PICOs 10 and 11 was judged to be very low despite the randomized design of
187 the COMFORT II trial, due to the limited size and lack of blindness of the study but even more due to the

severe indirectness provided by the low portion of actively treated patients in the BAT arm. No comparative evidence supporting a survival prolongation with ruxolitinib as compared with HU was available for patients with intermediate-1 disease (PICO 12). Similarly, no evidence supported a longer survival in patients treated with ruxolitinib versus interferon (PICOs 13 to 18).

Panel discussion

The panel judges that the universal prescription of a drug should be based on solid evidence supporting amelioration of one of the most relevant endpoint, which is survival. The panel, therefore deemed that the quality of available evidence for a survival benefit of ruxolitinib versus HU or interferon was not sufficient to support a recommendation.

Recommendations

The evidence supports a survival benefit associated with ruxolitinib but its quality according to GRADE was judged to be very low. Therefore, ruxolitinib should not be recommended uniquely for improving survival (weak recommendation).

Safety: bleeding and infection

Comparative safety of ruxolitinib and HU or interferon was available in the COMFORT II trial: 35 out of 146 (24%) patients assigned to ruxolitinib discontinued the therapy due to adverse events, as compared with only 4 out of 73 (5%) patients assigned to BAT.¹³ Safety outcomes were not judged to counterbalance the expected ruxolitinib benefit, however, the panel deemed that the reported safety could be reproduced in the clinical practice only if a proactive prevention of bleeding and infection was implemented.

Bleeding

Direct evidence of the relative safety of ruxolitinib versus HU was derived only from the COMFORT II trial: treatment interruptions due to adverse events were more frequent in patients assigned to ruxolitinib (8% versus 3%) as well as grade 3-4 thrombocytopenia (15% versus 5%) and overall bleeding events (odds ratio 2.2; 95% CI 1.3-2.7).^{4,13} Thanks to ruxolitinib dose-adjustment according to baseline and follow-up platelet count, severe bleeding was rarely reported (2% to 3%) either in the COMFORT trials or in the JUMP study, enrolling almost only patients with baseline platelet count higher than $100 \times 10^9/l$.^{4,5,13,16} Severe hemorrhages were also rare (less than 3%) in studies specifically enrolling patients with baseline platelet counts 50 to $100 \times 10^9/l$: 5 to 10 mg BID ruxolitinib were administered.²⁵⁻²⁷

The reported risk of bleeding related to ruxolitinib-induced thrombocytopenia prompted the panel to list

the principal bleeding risk factors: Table 3 lists such factors and the panel recommends a systematic assessment of these items before assigning any patient to ruxolitinib therapy. Moreover, the panel suggests periodical reassessment of these factors in treated patients. Physicians are advised to ensure patient awareness of his/her bleeding risk during the treatment. The panel did not provide any further suggestion on starting and continuation dose, which should be titrated based on platelet count, as reported by the product information.

Infection

The panel listed the most relevant issues to be considered in assessing infection risk (Table 4) and deemed that ruxolitinib could not be contraindicated in any specific subset of high-infective risk patients but that caution, specific monitoring or prophylactic measures are recommended in patients with at least one risk factor. Screening for hepatitis viruses was deemed mandatory in order to implement monitoring and/or prevention measures for potentially fatal reactivations. Specific anti-viral or anti-mycobacterial preventive measures have been proposed.^{9,28-29} The panel recommends the infection risk to be systematically assessed before administering ruxolitinib and caution in the prescription for patients carrying infection risk factors (Table 4). Prophylaxis for patients at high risk of viral or mycobacterial infections should be considered on a case to case basis. Moreover, physicians are advised to pursue patient awareness of his/her infective risk during the treatment.

Special subpopulations

Due to an overall lack of direct evidence of safety and efficacy, no evidence-based recommendations could be elaborated for the following specific subsets of patients.

Splanchnic vein thrombosis (SVT) and/or portal hypertension

Myelofibrosis patients with a history of SVT often have splenomegaly and also have a risk of portal hypertension with risk of variceal bleeding. They were identified as a special subpopulation. The panel elaborated safety recommendations based on eligibility criteria of a small phase II trial enrolling 21 patients with myeloproliferative neoplasms (including 12 MF) actively treated with anticoagulants or antiplatelet drugs and both showing a platelet count higher than $100 \times 10^9/l$ at baseline and esophageal varices of grade 2 or lower.³⁰ Ruxolitinib was administered at reduced doses for patients with a baseline platelet count lower than $200 \times 10^9/l$: 10 mg BID for PV, 15 mg BID for MF and 25 mg BID for ET. Despite the occurrence of grade 3-4 thrombocytopenia in 14.3% of the patients, accurate dose reductions limited bleeding events and only one episode of grade 2 upper gastrointestinal bleeding occurred during the study period. However, the reported background rate of major hemorrhage in this setting is quite low,

i.e. 3.6/100 patient-years.^{31,32} However, due to the large unmet needs of this patient subpopulation, the panel deemed not to recommend against ruxolitinib in this setting, but to use ruxolitinib with caution and to carefully titrate the dose with careful monitoring and management of portal hypertension. If ruxolitinib is used in these patients, patient awareness of bleeding risk is required.

Hepatomegaly

Some splenectomized patients have been reported as achieving a reduction of hepatomegaly during ruxolitinib treatment.^{33,34} The panel could not provide specific recommendations in favor or against the use of ruxolitinib in this subset of patients. However, the panel agreed that ruxolitinib can be considered in this clinical situation.

Comorbidities and limited-lifespan

The use of ruxolitinib was also questioned in patients with severe comorbidities which are expected to limit lifespan by themselves. Only a few patients aged over 80 years were enrolled into randomized COMFORT trials and the JUMP studies.^{4,5,16} Moreover, only 13% and 8% of patients assigned to ruxolitinib and BAT, respectively, showed a performance score ECOG 2 or higher.⁴ Comorbidities were not systematically reported by the COMFORT and the JUMP studies, but half of MF patients have a significant comorbidity burden in routine care.³⁵ No evidence of a clear benefit-to-risk ratio of ruxolitinib as compared with other available treatments has been reported in patients with limited lifespan or severe comorbidities. Therefore, the panel recommended avoidance of this drug in such patients, until favorable evidence is available.

Low-risk disease

The panel could not formulate any specific recommendation for the use of ruxolitinib in patients with low risk disease, due to insufficient evidence.

DISCUSSION

Ruxolitinib represents a novel therapeutic opportunity for patients with MF. However conflicting indications to its use in the clinical practice have been provided, some being based on disease risk and others on symptoms.^{7-9,36,37} In comparison with other published statements, the ELN-SIE panel chose to adopt the GRADE methodology to formulate evidence-based recommendation for an appropriate use of ruxolitinib. Evidence was retrieved and appraised for 18 PICOs (Table 1) and the panel subsequently formulated recommendations based on the benefit-to-risk profile of ruxolitinib, as compared with other available treatments. Six evidence-based recommendations were therefore formulated suggesting to use ruxolitinib for improving symptomatic or severe splenomegaly in patients with intermediate or high risk

281 disease not responsive to cytoreductive agents. Ruxolitinib was also strongly recommended in patients
282 with relevant disease-associated symptoms, provided that symptoms were adequately quantified and
283 classified. Therefore, a strong suggestion to ruxolitinib use was formulated only for patients scoring over
284 44 points by the MPN10; or suffering severe itching not responsive to standard therapy, or with either
285 unexplained fever or unintended weight loss. Due to the urgent need for treatment, despite the scarce
286 evidence, ruxolitinib was also recommended upfront for those patients with INT1 risk disease suffering
287 from both symptomatic and severe splenomegaly. The panel, however, chose not to recommend
288 ruxolitinib uniquely aimed at survival prolongation since no study has been designed and powered
289 sufficiently to provide definite evidence. This finally suggests to target therapeutic decisions on
290 symptoms and splenomegaly and not on survival. Such recommendations, however, also need to be
291 timely revised according to newly coming evidence.

292 ELN-SIE recommendations differ from those provided by the British Committee for Standards in
293 Hematology⁷ and by ESMO⁸. Both suggested ruxolitinib for patients with symptomatic splenomegaly or
294 constitutional symptoms but did not provide the physician with a detailed support for interpreting the
295 intensity and specificity of symptoms. ELN-SIE also struggled with using a solid methodology for
296 evidence appraisal. The whole decision process was tracked and summarized in the paper, in order to get
297 the best transparency and to provide the best evidence-to-recommendation adherence.

298 Despite the rigid GRADE methodology imposes a comparison between intervention and comparator
299 treatments, the huge and rapid improvement of symptoms reported during ruxolitinib treatment led the
300 panel to provide recommendations despite the scarce availability or poor quality of comparative
301 evidence. Rather, a strict comparison-based high quality evidence was requested by the panel for
302 considering ruxolitinib with the unique aim of improving survival. Therefore, the major result of this
303 project was a definite distinction between the enrollment criteria of the registration trials and the
304 decisional criteria for ruxolitinib prescription in clinical practice. Moreover, systematic and stringent
305 definitions of “relevant” symptoms or splenomegaly were provided, favoring a homogenous and non-
306 subjective assignment of the most suitable patients to ruxolitinib.

307 Some issues were not addressed, however, by the present project, such as the rules for treatment
308 discontinuation. IWG-MRT and ELN classified as “responsive” those patients achieving a 50% reduction of
309 disease-related symptoms as assessed with MPN10 or a 50% reduction of spleen size from left costal
310 margin.³⁸ A list of practical issues are faced in assessing the clinical response to ruxolitinib, such as
311 appropriate timing of response assessment in patients receiving full dose or suboptimal doses.³⁹ The
312 panel chose not to provide specific recommendations on the modality and timing of response

313 assessment or drug tapering before interruption. However, this was considered to be a relevant issue.
314 Furthermore, we did not include recommendations for ruxolitinib in patients who are candidates for
315 allogeneic SCT, since an EBMT/ELN consensus conference recently provided specific indications on
316 transplantation and peri-transplant therapies.⁴⁰ To be definitive on the role of ruxolitinib as bridge to
317 transplant, we decided to wait results from ongoing prospective trials. However, we have to mention
318 that the vast majority of patients with indications to allogeneic SCT are on ruxolitinib treatment. Nor
319 does this paper address combination therapies including ruxolitinib, since only preliminary data are
320 available from phase 1/2 studies. Finally, decision models estimated that ruxolitinib might reduce
321 disease-related costs in responders, but the overall value-for-cost of the drugs has not been completely
322 ascertained yet.⁴²⁻⁴³ Therefore, the present recommendations did not consider cost among the relevant
323 GRADE outcomes. However, the panel deemed that an appropriate clinical use of ruxolitinib should
324 assure a favorable value-for-cost.

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